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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,884	07/02/2003	Michael Houghton	PP19545.003	6634

27476 7590 03/30/2007

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,884	HOUGHTON, MICHAEL	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,11-14,16-24,41,42,45,47,49 and 59* is/are pending in the application.

4a) Of the above claim(s) *19-21 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-18,22-24,41,42,45,49 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's submission filed on January 8, 2007 has been entered. Claims 1-4, 11-14, 16-24, 41, 42, 45, 47, 49 and 59 are pending. Claims 19-21 and 47 remain withdrawn from consideration being drawn to non-elected subject matter. Claims 1-14, 11-14, 16-18, 22-24, 41, 42, 45, 49 and 59 remain under examination.

Claim Rejections - 35 USC § 103

2. The rejection of claims 1-4, 11-14, 16-18, 22-24, 41, 42, 45, 49 and 59 under 35 U.S.C. 103(a) as being unpatentable over Houghton et al. (US 5,683,864, "'864 Patent") in view of Houghton *et al.* (US 5,371,017, "Houghton") and Grakoui *et al.*, (Journal of Virology, 1993, 67(5):2832-2843, "Grakoui"), is maintained.

The Office notes that Paliard reference was erroneously included in the first sentence of the 103 rejection in the last Office action, July 31, 2006. Clearly, this reference to Paliard was a typographical error, as it was cited as a fragment, reproduced below:

> (*New Rejection*) Claims 1-4, 11-14, 16-18, 22-24, 41, 42, 45, 49 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houghton et al. (US 5,683,864, "'864 Patent" *et al.* (WO 01/30812 A2, "Paliard") in view of Houghton *et al.* (US 5,371,017, "Houghton") and Grakoui *et al.*, (Journal of Virology, 1993, 67(5):2832-2843, "Grakoui"). The claims are drawn to an immunogenic fusion protein comprising:

Paliard was cited in a previous 103 rejection, but deemed unavailable as prior art. The Office regrets any confusion that this may have caused. For clarification, the partial reference to the Paliard reference was mistakenly left in the first sentence of the rejection, however, the Paliard

reference was not relied upon in any way in the body of the rejection itself. The only references relied upon in the rejection of record were the '864 Patent, Houghton and Grakoui.

The claims are drawn to an immunogenic fusion protein comprising:

(a) a modified NS3 polypeptide comprising at least one amino acid substitution to the HCV NS3 region, such that protease activity is inhibited, and

(b) at least one polypeptide from a region of the HCV polyprotein other than the NS3 region, wherein the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein.

The modified NS3 polypeptide comprises a substitution of an amino acid corresponding to His-1083, Asp-1105 and/or Ser-1165, numbered relative to the full-length HCV-1 polyprotein. The fusion protein additionally comprises an NS4 polypeptide, an NS5a polypeptide, an NS5b polypeptide, and optionally a core polypeptide. The modified NS3 polypeptide and the other polypeptide are from the same HCV isolate, or from different isolates. The order of the proteins in the fusion protein from amino to carboxy terminal is: modified NS3 polypeptide, NS4 and NS5a. Another order is modified NS3 polypeptide, NS4, NS5a and NS5b. Another combination is modified NS3 polypeptide, NS4, NS5a and optionally, core polypeptide. Another combination is modified NS3 polypeptide, NS4, NS5a, NS5b and optionally, core polypeptide.

Also claimed are compositions comprising the fusion proteins described, in combination with a pharmaceutically acceptable excipient. Also claimed are methods of producing a composition comprising combining the immunogenic fusion protein with a pharmaceutically acceptable excipient. Claims 41, 42, 45 and 49 are drawn to compositions that optionally are

comprised of core polypeptide, wherein the core polypeptide comprises the sequence of amino acid depicted at amino acid position 1772-1892 of SEQ ID NO: 6.

The '864 Patent discloses combinations of HCV antigens from the C domain of the HCV polyprotein, and at least one additional HCV antigen from either the NS3 domain, the NS4 domain, the S domain or the NS5 domain. The antigens are in the form of a fusion protein which comprises a non-natural single continuous chain of amino acids (abstract and col. 3, lines 53-60). The '864 patent contemplates the use of HCV antigens from either the same source (isolate), or different sources (isolates), see col. 4, lines 29-37, and also col. 2, lines 26-28. Specific constructs of the fusion proteins are represented in the '864 Patent claims. Constructs that include the core polypeptide of HCV include amino acids 1-122 of the core polypeptide, which correspond with amino acids 1772-1892 of SEQ ID NO: 6 of the instant invention. The '864 Patent discloses that the fusion proteins are intended for use in immunoassays. While the '864 Patent does not specifically mention "pharmaceutically acceptable excipients", the media or buffer used to store the fusion proteins for the kit is a pharmaceutically acceptable excipient (col. 7, lines 10-20). The '864 Patent fails to teach an amino acid substitution(s) in the NS3 polypeptide rendering the protease (NS3) inhibited. The '864 Patent further fails to teach the specific substitutions.

However, Houghton teaches that the replacement of critical residue, serine, in the active site of the NS3 (protease) does not significantly alter the structure of the protease, and thus preserves binding specificity. Houghton teaches that the substituted protease retains its recognition and binding properties while failing to effect cleavage of the polyprotein (col. 3, lines 29-34, and col. 14, lines 32-48). With regard to the specific substitution, Grakoui discloses

the substitution of alanine for His-1083, Asp-1107 and Ser-1165 in HCV NS3, resulting in uncleaved NS domains. This activity qualifies as inhibited protease activity (abstract). While the substitution of alanine for Asp-1107 is not Asp-1105 (as claimed), position 1107 corresponds to the HCV-1 polyprotein, thus meeting the limitation of the claim.

It would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of the '864 Patent. One would have been motivated to render the protease (NS3) non-functional in order to avoid cleavage of the polyprotein, as taught by Houghton (col. 3, lines 29-34, and col. 14, lines 32-48). One would have been motivated to substitute the amino acids taught by Grakoui because Houghton discloses that certain substitutions result in the inhibition or ablation of protease function. One would have had a reasonable expectation that '864 Patent fusion protein would have worked with Houghton's NS3 amino acid substitution and Grakoui's substitution, because Grakoui demonstrates that the substitutions result in inhibited or non-existent protease activity. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time of the invention.

Response to Arguments

3. Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant asserts that there are no suggestions in the '864 Patent, Houghton or Grakoui to arrive at the claimed fusion proteins. Applicant asserts that the focus of the '864 Patent is immunoassays using combinations of HCV antigens for detection of anti-HCV antibodies. Applicant argues that the '864 Patent does not even mention

fusion proteins comprising an NS3 polypeptide modified to inhibit protease activity, let along any specific substitutions in the NS3 polypeptide that eliminate protease function.

- Applicant argues that there is no motivation to combine the teachings of Houghton and Grakoui with the '864 Patent. Although the Office has stated that it would have been obvious and that one would have had a reasonable expectation of success, Applicant argues that there is no motivation to combine.
  - In response to Applicant's arguments, the Office acknowledges the '864 Patent does not disclose modifying NS3 polypeptide to inhibit protease activity. Despite this deficiency in the '864 Patent, other references provide the necessary components to arrive at the claimed invention, relevant portions of which are reproduced (from the 103 rejection of record) below.
  - Houghton teaches that the replacement of critical residue, serine, in the active site of the NS3 (protease) does not significantly alter the structure of the protease, and thus preserves binding specificity. Houghton teaches that the substituted protease retains its recognition and binding properties while failing to effect cleavage of the polyprotein (col. 3, lines 29-34, and col. 14, lines 32-48). With regard to the specific substitution, Grakoui discloses the substitution of alanine for His-1083, Asp-1107 and Ser-1165 in HCV NS3, resulting in uncleaved NS domains. This activity qualifies as inhibited protease activity (abstract). While the substitution of alanine for Asp-1107 is not Asp-1105 (as claimed), position 1107 corresponds to the HCV-1 polyprotein, thus meeting the limitation of the claim.

- *It would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of the '864 Patent. One would have been motivated to render the protease (NS3) non-functional in order to avoid cleavage of the polyprotein, as taught by Houghton (col. 3, lines 29-34, and col. 14, lines 32-48). One would have been motivated to substitute the amino acids taught by Grakoui because Houghton discloses that certain substitutions result in the inhibition or ablation of protease function.*

- Applicant argues that the '864 Patent does not teach of suggest the use of fusion proteins in immunogenic composition and vaccines. Applicant argues that the second references, Houghton and Grakoui, fail to describe the claimed immunogenic fusion proteins. Houghton focuses on NS3 itself, but does not teach or suggest immunogenic fusion proteins comprising modified NS3 and other HCV polypeptides. Applicant argues that Grakoui pertains to polyprotein processing and identification of cleavage sites and residues that are critical for NS3 protease function. Applicant notes that Grakoui does not teach or suggest immunogenic compositions comprising fusion proteins for immunization against HCV.

  - In response to Applicant's arguments, the Office recognizes that the '864 Patent discloses that the fusion proteins are intended for use in immunoassays. While the '864 Patent does not suggest using the fusion proteins as immunogenic compositions, that does not alter the inherent immunogenicity of the fusion proteins. Whether one recognizes the fusion proteins as immunogenic, the fusion proteins are immunogenic. Note that the instant claims are drawn to products, or

methods of making the products. The claims under examination are not drawn to methods of using the products. Therefore, the rejection is maintained for reasons of record.

Conclusion

4. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 3/27/07

STACY B. CHEN
PRIMARY EXAMINER